

Amend claim 6 as follows:

6. (Once Amended) A [pharmaceutical composition] method according to claim 5, wherein the pharmaceutical composition contains [containing] 0.5 to 90% of said [active ingredient] 3'-deoxythymidin-2'-ene.

Amend claim 7 as follows:

7. A [pharmaceutical composition] method according to claim 5, wherein the pharmaceutical composition is in the form of a sterile physiologically isotonic aqueous solution.

Cancel claims 8, 9 and 10, without prejudice.

CONDITIONAL PETITION FOR EXTENSION OF TIME

If any extension of time for this response is required, applicants request that this be considered a petition therefore. Please charge the required Petition fee to Deposit Account No. 19-3869.

ADDITIONAL FEE

Please charge any insufficiency of fee, or credit any excess to Deposit Account No. 19-3869.

R E M A R K S

The Office Action dated July 13, 1987 has been carefully reviewed.

Reconsideration of the application, as amended, is respectfully requested.

Claims 5-8 and 9 were rejected under 35 U.S.C. 112, second paragraph for several reasons. In view of the above claim amendments, withdrawal of this rejection is earnestly solicited.

4 of the enclosed copy of Lin et al, "Potent and Selective In vitro Activity of 3'-Deoxythymidin-2'-ene (3'-Deoxy-2',3'-Didehydrothymidine) Against Human Immunodeficiency Virus".

Hence, the difference in antiviral activity against HIV-I of the saturated and unsaturated cytidine analogs differed by an insignificant factor of 2, whereas the unsaturated analog of thymidine is about 19-times more potent than the saturated analog. It was not obvious that such a marked increase in activity would have been observed based on what was found with the corresponding cytidine analogs.

The following papers, copies of which are enclosed, indicate variation in activity among different viruses:

(1) De Clercq , Journal of Antimicrobial Chemotherapy, 14, Suppl. A, 85-95 (1984) -see Table II on *J.T. 12-30-87*
page 88

(2) Biochemical Pharmacology, Vol. 29, pp. *J.T. 12-30-87*
1849-1851

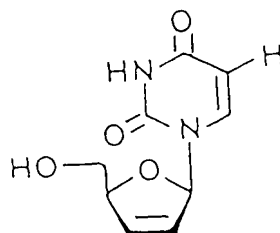
(3) Machida, Antimicrobial Agents and Chemotherapy, Vol. 29, No. 3, 524-526, Mar. 1986 *J.T. 12-30-87*

(4) De Clercq et al, J. Med. Chem., 29, 213-217, (1986) - see Table II on page 214. *J.T. 12-30-87*

The Examiner alleged that Verheyden et al teach the equivalents of 5-lower alkyl of 2',3'-unsaturated cytidin-2'-ene nucleosides. However, it is reported in Kim et al., J. Med. Chem., 30, 862, (1987), a copy of which is enclosed, that whereas 2',3'-dideoxycytidine is very active

against HIV-I, the insertion of a $-CH_3$ moiety in the 5-position abolished its antiviral activity against HIV-I and had increased cytotoxicity.

Furthermore, removal of the $-CH_3$ moiety of the subject compound results in the formation of 2',3'-dideoxy-2',3'-didehydrouridine, a compound which has no activity against HIV-I (Herdewijn et al., J. Med. Chem., 30, 1273, (1987), a copy of which is enclosed). Thus again, slight modifications of structure do not necessarily result in "obvious" results.



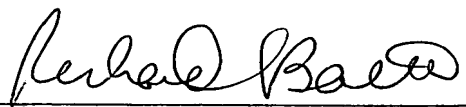
In view of the above, withdrawal of the rejection of claims under 35 U.S.C. 103 is earnestly requested.

The non-applied art is not believed to be as relevant as the art discussed above.

Applicants believe that this application is now in condition for allowance of all claims therein, and the early issuance of a Notice of Allowance is respectfully requested.

Respectfully submitted,

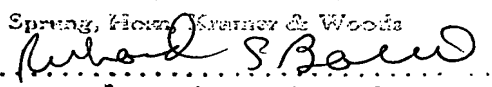
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I hereby certify that this correspondence is being deposited with the United States Postal Services as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231 on 06708 Oct 1, 1987.

Spring, Horn, Kramer & Woods
By 
Date 06708 Oct 1, 1987

Submitted to J. Med. Chem.

Synthesis and Antiviral Activity of Various 3' -Azido Analogues of Pyrimidine
Deoxyribonucleosides Against Human Immunodeficiency Virus (HIV-1, HTLV-III/LAV).

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Abstract

Various 3' -azido analogues of pyrimidine deoxyribonucleosides have been synthesized and tested against human immunodeficiency virus (HIV-1, HTLV-III/LAV) in human peripheral blood mononuclear cells. Among these compounds, the 3' -azido analogues of thymidine (2), 3-(3-oxo-1-propenyl)thymidine (21), 2' -deoxyuridine (1), 2' -deoxy-5-bromouridine (5), 2' -deoxy-5-fluorocytidine (19), 2' -deoxy-5-iodouridine (6), 2' -deoxycytidine (18), 2' -deoxy-5-fluorouridine (4), 2' -deoxy-5-(thiocyanato)uridine (16), 2' -deoxy-5-methylcytidine (20), 2' -deoxy-5-aminouridine (7), and 2' -deoxy-5-hydroxyuridine (10) were found to have significant antiviral activity, with EC₅₀ values of 0.002, 0.01, 0.2, 1.0, 1.0, 1.1, 1.2, 4.8, 5.1, 5.1, 6.2, and 10 μ M, respectively. The structure-activity relationships are discussed.

3'-Azido-3'-deoxythymidine (AZT) was found by Mitsuya *et al.*² to be a potent inhibitor of the replication of the human immunodeficiency virus (HIV), which is accepted to be responsible for the clinical syndrome termed AIDS. Furman *et al.*³ investigated the metabolism of AZT and found it to be sequentially phosphorylated to the 5'-mono-, -di- and -triphosphate analogues. As the triphosphate analog, AZT inhibits the utilization of dTTP by reverse transcriptase and may be incorporated in the terminal position of DNA thereby preventing elongation³. In either event the synthesis of HIV-1 DNA is prevented and hence inhibition of HIV-1 replication. Other sites of inhibition may also be involved however this has not been established. When AZT was combined with recombinant alpha A interferon a synergistic inhibition of HIV-1 in cell culture was found by Hartshorn *et al.*⁴, however, when combined with ribavirin Vogt *et al.*⁵ found it was antagonistic.

AZT in a preliminary 6-week clinical trial was reported by Yarchoan *et al.*⁶ to be well absorbed from the g.i. tract, to cross the blood brain barrier and to produce positive clinical improvement. Although AZT is not considered a cure, its ability to prolong life of AIDS patients, in spite of bone marrow suppression observed in some patients, has encouraged the evaluation of other nucleosides. AZT, as well as several other nucleoside analogs which are inhibitory to HIV-1 *in vitro*, were first synthesized by Horwitz *et al.*^{14,15}.

Several reviews have appeared recently which evaluate the various compounds for their activity against HIV-1, as well as a discussion of the AIDS problem in general¹⁶⁻¹⁹. The present report describes the synthesis of a variety of 3'-azido nucleosides, their antiviral activity against HIV-1 in cell culture, and a discussion of their structure activity relationship.

Chemistry

Various 3'-azido analogues of pyrimidine 2'-deoxyribofuranosyl nucleosides (Figure 1) have been synthesized and tested as potential anti-HIV agents. Compounds 1, 3, 4 - 6, and 18 - 20 were synthesized by the methodology previously described^{10,20,21}. Compound 2 was prepared by the methodology of Horwitz *et al.*¹⁵ with minor modification²². Treatment of 3'-azido-5'-O-acetyl-5-bromouridine¹⁰ with ammonia or other appropriate amines at 50-80°C in a stainless-steel container gave the respective 5-amino or alkylamino derivatives 7 - 9. Bromination²³ of 3'-azido-2',3'-dideoxyuridine (1)²⁰ with Br₂ - H₂O at room temperature, followed by treatment with MeOH - H₂O in the presence of

triethylamine produced 3'-azido-2',3'-dideoxy-5-hydroxyuridine 10. Alkylation of compound 10 with the appropriate alkyl halide (iodide, or bromide) in the presence of NaOH in MeOH - H₂O under N₂ afforded the corresponding 5-alkoxy analogues 11 - 15 (Scheme II).²⁴⁻²⁶ 3'-Azido-2',3'-dideoxy-5-(thiocyanato)uridine (16) was synthesized by reacting compound 1 with chlorothiocyanogen (ClSCN) which was prepared from chlorine and dry KSCN in glacial acetic acid²⁷. Treatment of compound 16 with dithiothreitol (DTT) in 0.1 M EDTA - MeOH (1:1), followed by methyl iodide in the presence of NaOH in MeOH - H₂O under N₂ yielded 3'-azido-2',3'-dideoxy-5-(methylmercapto)uridine 17 (Scheme III).^{28,29}

Treatment of 3'-azido-3'-deoxythymidine (2) with triethylamine in DMF at room temperature for one hour followed by propargylaldehyde at -78°C for two hours and then at room temperature overnight yielded the 3-oxo-1-propenyl derivative 21.

Tritylation of 6-azathymidine (22)³⁰ with trityl chloride in pyridine at 100°C gave the 5-O-trityl protected nucleoside 23 which was methanesulfonated with methanesulfonyl chloride in pyridine at 0-4°C. The resultant sulfonate 24 was then treated with lithium azide in DMF at 130°C to afford the 5'-O-trityl-3'-azido derivative 25. Detritylation of compound 25 with 80% acetic acid at 100°C produced 3'-azido-3'-deoxy-6-azathymidine 26 (Scheme IV).

Antiviral Activity

These compounds were tested against HIV-1 and the antiviral activity was expressed by the concentration (μM) that inhibits 50% of viral replication.

Among the 3'-azido analogues of pyrimidine deoxyribonucleosides, 3'-azido-3'-deoxythymidine (2, AZT) was the most active against HIV-1 *in vitro* with an EC₅₀ value of 0.002 μM. Conversely, 3'-azido-3'-deoxy-6-azathymidine (26) was practically inactive (EC₅₀>100 μM). The 3'-azido derivatives of 3-(3-oxo-1-propenyl)thymidine (21), 2'-deoxyuridine (1), 2'-deoxy-5-bromouridine (5), 2'-deoxy-5-fluorocytidine (19), 2'-deoxy-5-iodouridine (6), 2'-deoxycytidine (18), 2'-deoxy-5-fluorouridine (4), 2'-deoxy-5-(thiocyanato)uridine (16), 2'-deoxy-5-methylcytidine (20), 2'-deoxy-6-aminouridine (7), and 2'-deoxy-5-hydroxyuridine (10) also demonstrated significant antiviral activity with EC₅₀ values of 0.01, 0.2, 1.0, 1.0, 1.1, 1.2, 4.8, 5.1, 5.1, 6.2, and 10 μM, respectively. However, the 3'-azido derivatives of 2'-deoxy-5-[(cyanomethylene)oxy]uridine (15), 2'-deoxy-5-(2-propynyloxy)uridine (13), 2'-deoxy-5-(ethoxy)uridine (12), and 2'-deoxy-5-

(methoxy)uridine (11) only showed moderate antiviral activity with EC_{50} values of 16, 38, 54, and 70 μ M, respectively. The other 3'-azido derivatives in this series, compounds 3, 8, 9, 14, and 17, were found to be practically inactive ($EC_{50} > 100 \mu$ M). These compounds were not toxic to the host human PBM cell at $> 100 \mu$ M except compound 21 which was toxic at $\sim 10 \mu$ M. The results are summarized in Table I.

Structure - Activity Relationships

It appears that the substituents in the 5-position of the 2'-deoxynucleoside analogues affect the antiviral activity. These effects may be related to their substrate activity for thymidine kinase or cytidine kinase (for compounds 18 - 20), which is required for activation, or to differences in metabolic conversion to the di- or triphosphate, or to the relative affinity of the nucleoside analogue triphosphate for the reverse transcriptase.

Replacement of the hydrogen at carbon-5 of the uracil base in compound 1 with a methyl group produces the most active compound (2, AZT). Conversely, replacement of the hydrogen with a trifluoromethyl group (3) results in the loss of the antiviral activity. Whereas, substitution of the hydrogen at carbon-5 in 1 with a fluoro-, bromo-, iodo-amino-, hydroxyl- and thiocyanato group (compounds 4, 5, 6, 7, 10, and 16, respectively) retains a significant amount of antiviral activity. Substitution of the hydrogen in 5-amino and 5-hydroxyl group in compounds 7 and 10 with an alkyl group (methyl, ethyl, etc.) markedly reduces the antiviral activity. Substitution of the 3-N-hydrogen in the pyrimidine base in compound 2 with an 3-oxo-1-propenyl moiety produces the second most active compound (21) in this group. However, substitution of the carbon-6 in compound 2 with a nitrogen (26) results in the loss of antiviral activity. In the 2'-deoxycytidine series, replacement of the hydrogen at carbon-5 in compound 18 with a fluoro group (19) yields a compound with equal antiviral activity. Substitution of the hydrogen with a methyl group (20), however, results in the reduction of antiviral activity. There seems to be no clear relationship between the antiviral activity, and either the electron-withdrawing or the electron-donating capacity of the substituents in the 5-position of the nucleoside analogues.

Experimental Section

Melting points were determined with a Thomas-Hoover Unimelt apparatus and are uncorrected. ^1H NMR spectra were recorded at 500 MHz on a Bruker WM-500 spectrometer

with Me₄Si as the internal reference. The UV spectra were recorded on a Beckman-25 spectrophotometer. IR spectra were taken on the Perkin-Elmer 21 spectrophotometer. The mass spectra (at 70 eV) were provided by Yale University Chemical Instrumentation Center. TLC was performed on EM precoated silical gel sheets containing a fluorescent indicator. Elemental analyses were carried out by the Baron Consulting Co., Orange, CT. Where analyses are indicated only by symbols of the elements, the analytical results obtained for those elements were within $\pm 0.4\%$ of the theoretical values.

3' -Azido-2' ,3' -dideoxy-5-aminouridine hydrochloride (7)

Liquid ammonia (70 mL) was added to 3' -azido-2' ,3' -dideoxyuridine ²⁰ (1, 2.5g, 6.70 mmol) in a stainless-steel container. The container was sealed and kept at $\sim 50^{\circ}\text{C}$ for 24 h. The excess ammonia was allowed to evaporate by blowing over dry N₂. The brown residue was dissolved in 50 mL of 0.1N hydrochloric acid, and the solution was passed through a column (2 x 20 cm) packed with Dowex 50-X8(H⁺) ion-exchange resin. The column was first eluted with H₂O to remove any unreacted starting material and other by-products, and then eluted with 0.5 N hydrochloric acid. Fractions containing the product, as determined by TLC (CH₂Cl₂ - MeOH, 7:3, R_f 0.75) were combined and evaporated in vacuo at $<40^{\circ}\text{C}$ to a volume of ~ 15 mL. Addition of methanol (40 mL) to the solution caused immediate formation of colorless crystals of 7 which were collected by filtration: yield, 0.60 g (30%); mp 215-218 $^{\circ}\text{C}$ (dec); IR (KBr) 4.76 μm (azido); UV (EtOH) λ_{max} 297nm; λ_{min} 257nm; NMR (Me₂SO-d₆) δ 2.34 - 2.36 (m, 2H, 2' -H), 3.63 - 3.66 (m, 2H, 5' -H), 3.93 (q, 1H, 4' -H), 4.39 (q, 1H, 3' -H), 4.2 - 5.0 (br s, 1H, 5' -OH, D₂O exchangeable), 6.02 (t, 1H, 1' -H), 8.31 (s, 1H, 6' -H), 8.80 - 10.4 (br s, 3H, 5-NH⁺₃, D₂O exchangeable), 12.0 (s, 1H, 3-NH, D₂O exchangeable); MS m/e 269 (M⁺-HCl). Anal. (C₉H₁₂N₆O₄ HCl) C, H, N.

Compounds 8 and 9 were synthesized by the same methodology as described for the preparation of compound 7 except that the appropriate amines were used and the reaction temperature was maintained at $\sim 80^{\circ}\text{C}$.

3' -Azido-2' ,3' -dideoxy-5-(methylamino)uridine hydrochloride (8): mp 184-187 $^{\circ}\text{C}$ (dec); IR (KBr) 4.77 μm (azido); UV (0.01 N HCl) λ_{max} 266 nm (ϵ 11,300), λ_{min} 232 nm, shoulder at 304 nm; UV (0.01 N NaOH) λ_{max} 293 nm (ϵ 8,400), λ_{min} 263 nm. NMR (Me₂SO-d₆) δ 2.30 - 2.35 (m, 1H, 2' -H_a), 2.38-2.44 (m, 1H, 2' -H_b), 2.67 (s, 3H, 5-N-CH₃), 3.60-3.63 (m, 1H, 5' -H_a), 3.66-3.69 (m, 1H, 5' -H_b), 3.89 (m, 1H, 4' -H), 4.40 (q, 1H, 3' -H), 4.80-6.30 (br s, 3H, 5' -OH and 5-NH⁺₂, D₂O exchangeable), 6.06 (t, 1H, 1' -H), 7.86 (s, 1H, 6-H), 11.8 (s, 1H, 3-NH, D₂O exchangeable); MS m/e 283 (M⁺-HCl). Anal. (C₁₀H₁₄N₆O₄ HCl) C,H,N.

3'-Azido-2',3'-dideoxy-5-(dimethylamino)uridine hydrochloride (9): mp 205-208°C (dec); IR (film) 4.75 μm (azido); UV (EtOH) λ_{max} 299nm, λ_{min} 264 nm; NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.34-2.42 (m, 1H, 2' -H_a), 2.43-2.46 (m, 1H, 2' -H_b), 2.55 [s, 6H, 5-N (CH_3)₂], 3.61-3.65 (m, 1H, 5' -H_a), 3.69-3.72 (m, 1H, 5' -H_b), 3.90 (m, 1H, 4' -H), 4.42 (q, 1H, 3' -H), 4.60-6.00 (br s, 2H, 5' -OH and 5-NH⁺, D₂O exchangeable), 6.05 (t, 1H, 1' -H), 8.22 (s, 1H, 6-H), 11.9 (s, 1H, 3-NH, D₂O exchangeable); Ms m/e 297 (M⁺-HCl). Anal. ($\text{C}_{11}\text{H}_{16}\text{N}_6\text{O}_4 \text{HCl}$) C, H, N.

3'-Azido-2',3'-dideoxy-5-hydroxyuridine (10)

Bromine was added dropwise to a stirred solution of 3'-azido-2',3'-dideoxyuridine (1, 3.0g, 11.9 mmol) in 60 mL of H₂O and 40 mL of THF at room temperature until a light-yellow color persisted (ca. 0.8 mL of bromine). Air was then bubbled through the solution until it became almost colorless. The solution was cooled in an ice-water bath and 90 mL of triethylamine was added in several portions so that the temperature of the solution did not exceed 25°C. The resulting solution was kept overnight, and evaporated under diminished pressure (water pump) below 40°C to dryness. The residue was chromatographed twice on a silica gel column (CH_2Cl_2 -MeOH, 5:1, R_f 0.69) to afford 0.65g (20%) of the desired product: mp 193° (dec); IR (film) 4.80 μm (azido); UV (EtOH) λ_{max} 282 nm, λ_{min} 248 nm; NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.21-2.26 (m, 1H, 2' -H_a), 2.31-2.37 (m, 1H, 2' -H_b), 3.61 (m, 2H, 5' -H), 3.82 (m, 1H, 4' -H), 4.38 (m, 1H, 3' -H), 5.20 (s, 1H, 5-OH, D₂O exchangeable), 6.10 (t, 1H, 1' -H), 7.33 (s, 1H, 6-H), 8.70 (s, 1H, 5' -OH, D₂O exchangeable), 11.5 (s, 1H, 3-NH, D₂O exchangeable); MS m/e 270 (M⁺ + 1). Anal. ($\text{C}_9\text{H}_{11}\text{N}_5\text{O}_5$), C, H, N.

3'-Azido-2',3'-dideoxy-5-(methoxy)uridine (11)

To a stirred solution of 3'-azido-2',3'-dideoxyuridine (1, 2.0g, 7.9 mmol) in a mixture of 25 mL of THF and 40 mL of H₂O at room temperature, bromine was added dropwise until a light-yellow color persisted. Air was then bubbled through the solution until it became almost colorless. Triethylamine (30 mL) and methanol (10 mL) were added to the clear solution (cooled in an ice-water bath). The resultant solution was kept at room temperature for 4 h and then evaporated in vacuo below 40°C to dryness. The residue (compound 10) was used for the next step without further purification.

The above residue was dissolved in a mixture of MeOH (25 mL) and H₂O (17 mL), to which 8 mL of 1N NaOH were added. Methyl iodide (5.7g, 40 mmol, 2.5 mL) was added to the solution. The reaction mixture was allowed to proceed for seven days at room temperature, and the progress was monitored by TLC (EtOAc - hexane, 5:1, R_f 0.78). The solvents were removed in vacuo (~40°C). The residue was chromatographed on a silica gel column (EtOAc

- Hexane, 2:1) to afford 0.17 g (8% based on 1) of product: mp 116-118°C; IR(film) 4.83 μm (azido); UV (EtOH) λ_{max} 280 nm, λ_{min} 242 nm; NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.33-2.37 (m, 1H, 2' -H_a), 2.44-2.48 (m, 1H, 2' -H_b), 3.20 (s, 3H, 5-OCH₃), 3.61 (m, 1H, 5' -H_a), 3.69 (m, 1H, 5' -H_b), 3.86 (m, 1H, 4' -H), 4.37 (q, 1H, 3' -H), 5.39 (t, 1H, 5' -OH, D₂O exchangeable), 6.04 (t, 1H, 1' -H), 8.45 (s, 1H, 6-H); MS m/e 283 (M⁺), 268 (M⁺-CH₃). Anal (C₁₀H₁₃N₅O₅) C, H, N.

Compounds 12 - 15 were synthesized by the same methodology as described for the synthesis of compound 11, except that the appropriate alkyl halides (bromide or iodide) were employed, and in some cases the reaction time was shorter.

3' -Azido-2',3' -dideoxy-5-(ethoxy)uridine (12): mp 118-120°C; IR (film) 4.82 μm (azido); UV (EtOH) λ_{max} 281 nm, λ_{min} 242 nm; NMR ($\text{Me}_2\text{SO}-d_6$) δ 1.24 (t, 3H, -CH₃), 2.25-2.28 (m, 1H, 2' -H_a), 2.39-2.42 (m, 1H, 2' -H_b), 3.60-3.62 (m, 1H, 5' -H_a), 3.65 - 3.68 (m, 1H, 5' -H_b), 3.83 (m, 1H, 4' -H), 3.80 (q, 2H, OCH₂-), 4.41 (m, 1H, 3-H), 5.31 (t, 1H, 5' -OH, D₂O exchangeable), 6.11 (t, 1H, 1' -H), 7.53 (s, 1H, 6-H), 11.5 (s, 1H, 3-NH, D₂O exchangeable); MS m/e 297 (M⁺), 298 (M⁺ + 1). Anal (C₁₁H₁₅N₅O₅) C, H, N.

3' -Azido-2',3' -dideoxy-5-(2-propynyloxy)uridine (13):

The reaction time for the synthesis of this compound was 36 h; mp 208-211°C (dec); IR (film) 4.80 μm ; UV (EtOH) λ_{max} 278 nm, λ_{min} 238 nm; NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.28-2.31 (m, 1H, 2' -H_a), 2.36-2.39 (m, 1H, 2' -H_b), 2.66 (m, 1H, CH), 3.84 (m, 1H, 4' -H), 4.41 (m, 1H, 3' -H), 4.60 (s, 2H, OCH₂-), 5.27 (t, 1H, 5' -OH, D₂O exchangeable), 6.11 (t, 1H, 1' -H), 7.86 (s, 1H, 6-H), 11.6 (s, 1H, 3-NH); MS m/e 308 (M⁺ + 1); Anal. (C₁₂H₁₃N₅O₅) C, H, N.

3' -Azido-2',3' -dideoxy-5-(propenyloxy)uridine (14):

The reaction time was 24 h for the synthesis of this compound; mp 164°C (dec); IR (film) 4.80 μm (azido); UV (EtOH) λ_{max} 280 nm, λ_{min} 243 nm; NMR (CDCl_3) δ 2.40 - 2.50 (m, 2H, 2' -H), 3.82 (m, 1H, 4' -H), 3.95 - 4.05 (m, 2H, 5' -H), 4.36 - 4.40 (q, 1H, 3' -H), 4.43 (m, 2H, OCH₂-), 4.44 (m, 1H, 5' -OH, D₂O exchangeable), 5.27 - 5.38 (m, 2H, C=CH₂), 5.92 - 6.00 (m, 1H, - C - CH = C), 6.15 (t, 1H, 1' -H), 7.40 (s, 1H, 6-H), 8.20 - 9.80 (br s, 1H, 3-NH, D₂O exchangeable); MS m/e 309 (M⁺), 310 (M⁺ + 1). Anal. (C₁₂H₁₅N₅O₅) C, H, N.

3'-Azido-2',3'-dideoxy-5-[(cyanomethylene)oxy]uridine (15):

The reaction time was 48 h for the synthesis of this compound; mp 161-163°C (dec); IR (film) 4.77 μm (azido); UV (EtOH) λ_{max} 273 nm, λ_{min} 237 nm; NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.28 - 2.33 (m, 1H, 2' - H_a), 2.38 - 2.42 (m, 1H, 2' - H_b), 3.56 - 3.68 (m, 2H, 5' -H), 3.86 (m, 1H, 4' -H), 4.41 (q, 1H, 3' -H), 4.92 (s, 2H, OCH_2CN), 5.30 (t, 1H, 5' -OH, D_2O exchangeable), 6.06 (t, 1H, 1' -H), 7.90 (s, 1H, 6-H), 11.7 (s, 1H, 3-NH, D_2O exchangeable); MS m/e 307 (M^+-1), 308 (M^+). Anal. ($\text{C}_{11}\text{H}_{12}\text{N}_6\text{O}_5$) C, H, N.

3'-Azido-2',3'-dideoxy-5-(thiocyanato)uridine (16):

3'-Azido-2',3'-dideoxyuridine (1, 0.9g, 3.6 mmol) was dried for two hours at 100°C in vacuo and then added to a solution of ClSCN which was prepared from chlorine (3.6g, 50 mmol) and dry KSCN (5.4g, 55 mmol) in 200 mL of glacial acetic acid. The reaction was conducted under anhydrous conditions and stirred at room temperature. The progress of the reaction was monitored by TLC. As soon as TLC showed the complete disappearance of the starting material (compound 1) (EtOAc - hexane, 4:1, R_f 0.24), the reaction was terminated by adding cyclohexane (10 mL) and stirring for 20 min. The reaction mixture was filtered, and the filtrate was evaporated to dryness in vacuo at <40°C. The residue was extracted with ether, and the insoluble material was dissolved in MeOH, and chromatographed on a silica gel column (EtOAc - hexane, 4:1, R_f 0.61) to give 0.18 g (16%) of the product: mp 144 - 146°C (dec); IR (film) 4.76 μm (azido); UV (EtOH) λ_{max} 275 nm, λ_{min} 238 nm; NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.34 - 2.38 (m, 1H, 2' - H_a), 2.47 - 2.49 (m, 1H, 2' - H_b), 3.60 (m, 1H, 5' - H_a), 3.70 (m, 1H, 5' - H_b), 3.86 (q, 1H, 4' -H), 4.36 (q, 1H, 3' -H), 5.41 (t, 1H, 5' -OH, D_2O exchangeable), 5.99 (t, 1H, 1' -H), 8.65 (s, 1H, 6-H), 12.0 (s, 1H, 3-NH, D_2O exchangeable); MS M/e 308 (M^+-2), 309 (M^+-1), 310 (M^+). Anal. ($\text{C}_{10}\text{H}_{10}\text{N}_6\text{O}_4\text{S}$) C, H, N.

3'-Azido-2',3'-dideoxy-5-(methylmercapto)uridine (17)

3'-Azido-2',3'-dideoxy-5-(thiocyanato)uridine (16, 90 mg 0.20 mmol) was dissolved in 10 mL of 0.1 M EDTA (pH 7.8) and 10 mL of MeOH and then dithiothreitol (DTT, 100 mg, 0.65 mmol) was added to the solution. When the reaction was completed as monitored by the appearance of the 332 nm band in the UV spectrum, the resulting colorless solution was evaporated to dryness in vacuo at <40°C. The residue was suspended in MeOH with stirring, and then filtered. The filtrate was concentrated to ~3 mL and filtered again. Under an atmosphere of N_2 the filtrate was diluted with MeOH to 10 mL and 5 mL of H_2O and 4 mL of 0.1 N NaOH was added followed by 0.1 mL of CH_3I (0.23g, 1.6 mmol).

The reaction mixture was stirred at room temperature overnight under and atmosphere of N_2 . Evaporation of the solvents in vacuo afforded a white solid which was chromatographed on a silica gel column (EtOAc-hexane, 3:1, R_f 0.43), and then rechromatographed on a preparative TLC plate (2mm) twice to give 18 mg (20% based on **16**) of product: mp 115-118°C; IR (film) 4.80 μ m (azido); UV (EtOH) λ_{max} 291 nm, λ_{min} 261 nm; NMR (Me_2SO-d_6) δ 2.18 (s, 3H, 5- CH_3), 2.18 - 2.23 (m, 1H, 2'- H_a), 2.32 - 2.37 (m, 1H, 2'- H_b), 3.60 (m, 2H, 5'-H), 3.81 (m, 1H, 4'-H), 4.39 (q, 1H, 3'-H), 5.29 (br s, 1H, 5'-OH, D_2O exchangeable), 6.13 (t, 1H, 1'-H), 7.53 (s, 1H, 6-H), 11.0 - 12.0 (br s, 3-NH, D_2O exchangeable); MS m/e 299 (M^+), 300 ($M^+ + 1$). Anal ($C_{10}H_{13}N_5O_4S$) C, H, N.

3-(3-Oxo-1-propenyl)-3'-azido-3'-deoxythymidine (21)

3'-Azido-3'-deoxythymidine (**2**, 1.0g, 3.7 mmol) was dissolved in anhydrous DMF (3 mL) containing triethylamine (0.52g, 3.7 mmol), and the mixture was stirred for 1 h at room temperature. The solution was cooled to -78°C (acetone - dry ice bath), and propargylaldehyde (6.3g, ~100 mmol) was added in one portion. The reaction mixture was stirred at -78°C for 2 h and then allowed to come up to room temperature slowly overnight. Excess reagents and DMF were removed in vacuo, and the residue was chromatographed on a silica gel column (EtOAc - hexane, 2:1). The product was obtained as almost colorless needles. (0.15 g, 13%): mp 107-108°C; TLC R_f 0.6 (EtOAc - hexane, 2:1); IR (film) 4.85 μ m (azido); UV (EtOH) λ_{max} 267 nm, λ_{min} 235 nm; NMR (Me_2SO-d_6) δ 2.34 - 2.40 (m, 1H, 2'- H_a), 2.44 - 2.49 (m, 1H, 2'- H_b), 3.61 - 3.64 (m, 1H, 5'- H_a), 3.68 - 3.72 (m, 1H, 5'- H_b), 3.88 (m, 1H, 4'-H), 4.40 (q, 1H, 3'-H), 5.31 (t, 1H, 5'-OH, D_2O exchangeable), 6.11 (t, 1H, 1'-H), 7.07 (q, 1H, =CH-), 7.91 (s, 1H, 6-H), 8.16 (d, 1H, N-CH=), 9.61 (d, 1H, -CHO); MS m/e 322 ($M^+ + 1$). Anal. ($C_{13}H_{15}N_5O_5$) C, H, N.

6-Azathymidine (22): mp 150 - 153°C (lit ³⁰ mp 153-154°C); NMR (Me_2SO-d_6) δ 2.03 (m, 1H, 2'- H_a), 2.10 (s, 3H, 5- CH_3), 2.40 (m, 1H, 2'- H_b), 3.34 (dd, 1H, 5'- H_a), 3.46 (dd, 1H, 5'- H_b), 3.68 (dd, 1H, 4'-H), 4.27 (dd, 1H, 3'-H), 4.60 (br s, 1H, 5'-OH, D_2O exchangeable), 5.13 (br s, 1H, 3'-OH, D_2O exchangeable), 6.31 (dd, 1H, 1'-H) 11.9 (br s, 1H, 3-NH, D_2O exchangeable).

5'-O-Trityl-6-azathymidine (23)

A solution of 6-azathymidine (**23**, 0.6g, 2.5 mmol) and triphenylmethyl chloride (0.7g, 0.25 mmol) in 70 mL of pyridine was heated with stirring at ~100°C for 1 h. The

reaction mixture was evaporated in vacuo to give a syrup which was triturated with H_2O . The resulting solid was collected by filtration, and recrystallized from CH_2Cl_2 to yield 0.6g (40%) of product: mp 105-108°C, NMR ($\text{Me}_2\text{SO}-d_6$) δ 2.00 (s, 3H, 5- CH_3), 2.08 (m, 1H, 2'- H_a), 2.36 (m, 1H, 2'- H_b), 3.03 (m, 2H, 5'-H), 3.94 (m, 1H, 4'-H), 4.25 (m, 1H, 3'-H), 5.11 (d, 1H, 3'-OH, D_2O exchangeable), 6.16 (dd, 1H, 1'-H), 7.10 - 7.20 (m, 15H, phenyl), 12.1 (br s, 1H, 3-NH, D_2O exchangeable); MS m/e 485 (M^+). Anal. ($\text{C}_{28}\text{H}_{27}\text{N}_3\text{O}_5$) C, H, N.

3'-Azido-3'-deoxy-5'-O-trityl-6-azathymidine (25)

Methanesulfonyl chloride (1.47g, 12.8 mmol) was added to a solution of compound 24 (0.13g, 0.30 mmol) in 15 mL of pyridine. The reaction mixture was stirred at 4°C for 20 h and then the solvent was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (25 mL) and the solution was washed with NaHCO_3 solution, H_2O , and dried over anhydrous Na_2SO_4 . The solvent was removed under diminished pressure to give a syrup (compound 24) which was used in the following reaction without further purification.

A solution of compound 24 (0.41g, 0.72 mmol) and lithium azide (0.30g, 7.2 mmol) in 20 mL of DMF was heated with stirring at 130°C (oil bath) for 2 h. The reaction mixture was then poured into ice-water and extracted several times with CH_2Cl_2 . The combined CH_2Cl_2 solution was dried over anhydrous Na_2SO_4 , and evaporated to dryness in vacuo. The resulting syrup was chromatographed on a preparative silica gel plate (2 mm) ($\text{EtOAc} - \text{CH}_2\text{Cl}_2$, 1:2) to afford 0.13 g (33%) of product: mp 83-85°C; IR (film) 4.75 μm (azido); NMR ($\text{Me}_2\text{SO}-d_6$) δ 1.86 (s, 3H, 5- CH_3), 2.30 (m, 1H, 2'- H_a), 2.55 (m, 1H, 2'- H_b), 3.16 (m, 2H, 5'-H), 3.98 (m, 1H, 4'-H), 4.40 (m, 1H, 3'-H), 6.16 (dd, 1H, 1'-H), 7.10 - 7.20 (m, 15H phenyl), 12.1 (br s, 1H, 3-NH, D_2O exchangeable); MS m/e 510 (M^+). Anal. ($\text{C}_{28}\text{H}_{26}\text{N}_6\text{O}_4$) C, H, N.

3'-Azido-3'-deoxy-6-azathymidine (26)

Compound 25 (0.22g, 0.40 mmol) in 20 mL of 80% acetic acid was heated with stirring for 20 min. The solution was evaporated to dryness, and the residue chromatographed on a preparative silica gel plate (2 mm) ($\text{EtOAc} - \text{CH}_2\text{Cl}_2$, 1:2). The product was isolated as a glass and weighed 0.1g (86%): IR (film) 4.75 μm (azido); UV (EtOH) λ_{max} 264 nm, λ_{min} 226 nm; NMR (CDCl_3) δ 2.18 (s, 3H, 5- CH_3), 2.31 (m, 1H, 2'- H_a), 2.68 (m, 1H, 2'- H_b), 3.65 (m, 1H, 5'- H_a), 3.84 (m, 1H, 5'- H_b), 3.96 (m, 1H, 4'-H), 4.37 (m, 1H, 3'-H), 5.10 (brs, 1H, 5'-OH, D_2O exchangeable), 6.42 (dd, 1H, 1'-H). MS m/e 269 ($\text{M}^+ + 1$), 270 ($\text{M}^+ + 2$).

Antiviral Test Procedures

Three-day-old mitogen-stimulated human peripheral blood mononuclear cells (10^6 cells/mL) were infected with HIV-1 (strain LAV) at a concentration of about 100 TCID₅₀ per mL and cultured in the presence and absence of various concentrations of compounds. The drugs were added about 45 min after infection. Five days after infection the supernatant was clarified and the virus pelleted. The reverse transcriptase activity in the disrupted virus was determined. The methods used for culturing the PBM cells, harvesting the virus and determining the reverse transcriptase activity were those described by McDougal *et al.*³³ and Spira *et al.*³⁴ The virus infected control had about 2×10^5 dpm per ml of reverse transcriptase activity. The blank and uninfected cell control values were about 300 and 1000 dmp, respectively. Drugs with potent activity were retested using different PBM cells.

The effects of the drugs on the growth of uninfected human PBM cells were also established. Mitogen-stimulated PBM cells (3.8×10^5 cells/mL) were cultured in the presence and absence of drugs under the same conditions as those used for the antiviral assays described above. The cells were counted daily for five days using the trypan blue exclusion method. The EC₅₀ was determined by the median effect method³⁵.

Acknowledgments

This research was supported by United States Public Health Service Grants CA-05262, CA-28852 and CA-44094 from the National Cancer Institute and by a Merit Award from the Veterans Administration. The technical assistance of D. Mozdiesz is gratefully acknowledged.

References and Notes

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Table I. Antiviral Activity of Various 3'-Azido Analogues of Pyrimidine Deoxyribonucleosides on the Replication of Human Immunodeficiency Virus (HIV-1, HTLV-III/LAV) in Human Peripheral Blood Mononuclear Cells

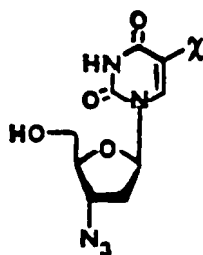
Compd.	EC ₅₀ μM (HIV-1)
✓ 1	0.2 ³²
✓ 2	0.002 (0.23) ¹⁰
✓ 3	>100
4	4.8
5	1.0 (2.3) ¹⁰
6	1.1
7	6.2
8	>100
9	>100
10	~10
11	70
12	54
13	38
14	>100
15	16
16	5.1
17	>100
18	1.2
19	1.0
20	5.1
21	0.01
26	>100

Elemental Analyses Data

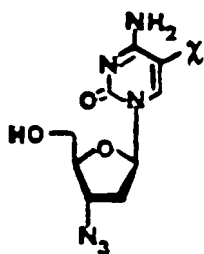
<u>Compd.</u>	<u>Calcd.</u>	<u>Found</u>
<u>7</u>	%C: 35.47 %H: 4.30 %N: 27.58	35.33 4.32 27.84
<u>8</u>	%C: 37.75 %H: 4.74 %N: 26.37	37.61 4.66 26.65
<u>9</u>	%C: 39.70 %H: 5.15 %N: 25.26	39.64 5.33 25.53
<u>10</u>	%C: 40.15 %H: 4.12 %N: 26.01	40.15 3.99 26.39
<u>11</u>	%C: 42.41 %H: 4.63 %N: 24.72	41.87 4.44 24.59
<u>12</u>	%C: 44.44 %H: 5.08 %N: 23.56	44.19 4.78 23.67
<u>13</u>	%C: 46.90 %H: 4.23 %N: 22.80	46.52 4.45 22.47

Elemental Analyses Data cont'd.

<u>Compd.</u>	<u>Calcd.</u>	<u>Found</u>
<u>14</u>	%C: 46.56 %H: 4.88 %N: 22.64	46.85 5.12 22.54
<u>15</u>	%C: 42.86 %H: 3.93 %N: 27.26	42.79 3.94 26.99
<u>16</u>	%C: 38.67 %H: 3.25 %N: 27.08	38.28 2.99 26.88
<u>17</u>	%C: 40.13 %H: 4.35 %N: 23.41	40.52 4.08 23.74
<u>21</u>	%C: 48.60 %H: 4.71 %N: 21.80	48.61 4.65 21.52
<u>23</u>	%C: 69.29 %H: 5.57 %N: 8.66	69.42 5.21 8.35
<u>25</u>	%C: 65.88 %H: 5.10 %N: 16.47	65.49 5.43 16.06



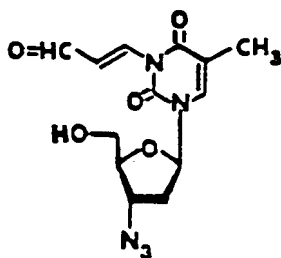
- | | |
|--|---|
| ✓ 1: $\chi = \text{H}$ | 10: $\chi = \text{OH}$ |
| 2: $\chi = \text{CH}_3$ | 11: $\chi = \text{OCH}_3$ |
| ✓ 3: $\chi = \text{CF}_3$ | 12: $\chi = \text{OCH}_2\text{CH}_3$ |
| 4: $\chi = \text{F}$ | 13: $\chi = \text{OCH}_2\text{C}\equiv\text{CH}$ |
| 5: $\chi = \text{Br}$ | 14: $\chi = \text{OCH}_2\text{CH}=\text{CH}_2$ |
| 6: $\chi = \text{I}$ | 15: $\chi = \text{OCH}_2\text{CN}$ |
| 7: $\chi = \text{NH}_2\cdot\text{HCl}$ | 16: $\chi = \text{SCN}$ |
| 8: $\chi = \text{NHCH}_3\cdot\text{HCl}$ | 17: $\chi = \text{SCN}$ ^{H₃} N₃ |
| 9: $\chi = \text{N}(\text{CH}_3)_2\cdot\text{HCl}$ | |



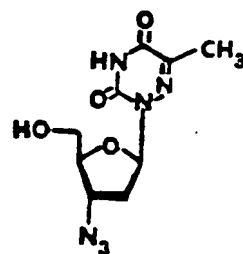
18: $\chi = \text{H}$

19: $\chi = \text{F}$

20: $\chi = \text{CH}_3$



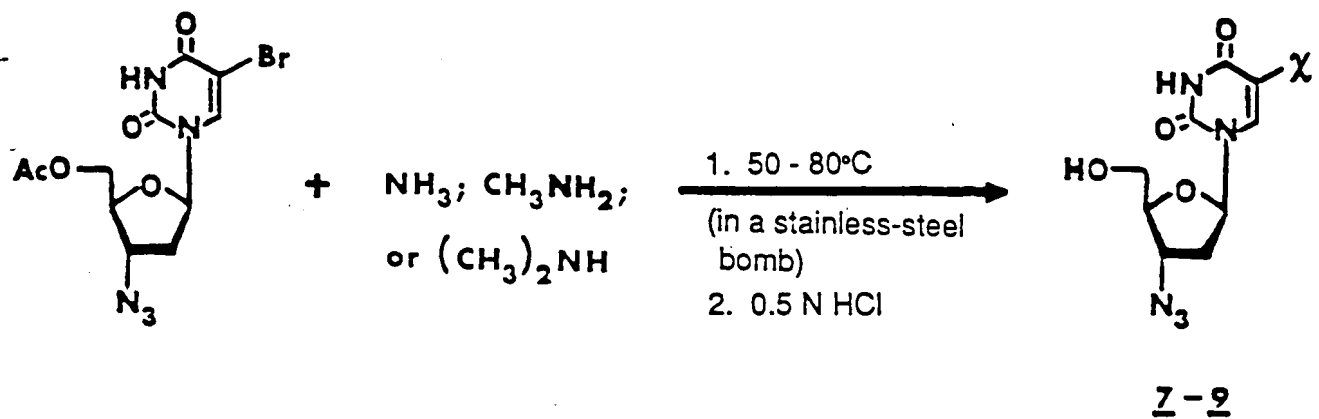
21



26

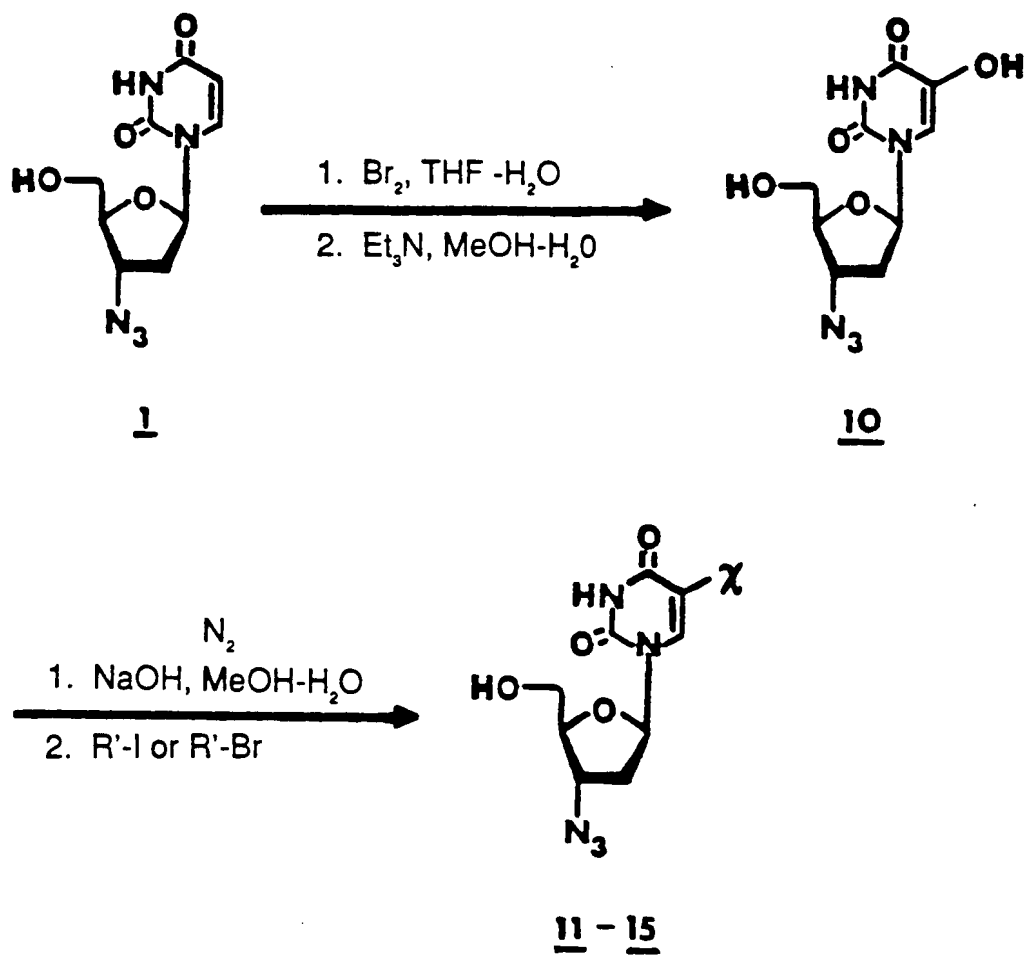
FIGURE 1. Structure formulae of various 3'-azido analogues of pyrimidine deoxyribonucleosides.

Scheme 1



$\chi = \text{NH}_2 \cdot \text{HCl}, \text{NHCH}_3 \cdot \text{HCl},$
 $\text{N}(\text{CH}_3)_2 \cdot \text{HCl}$

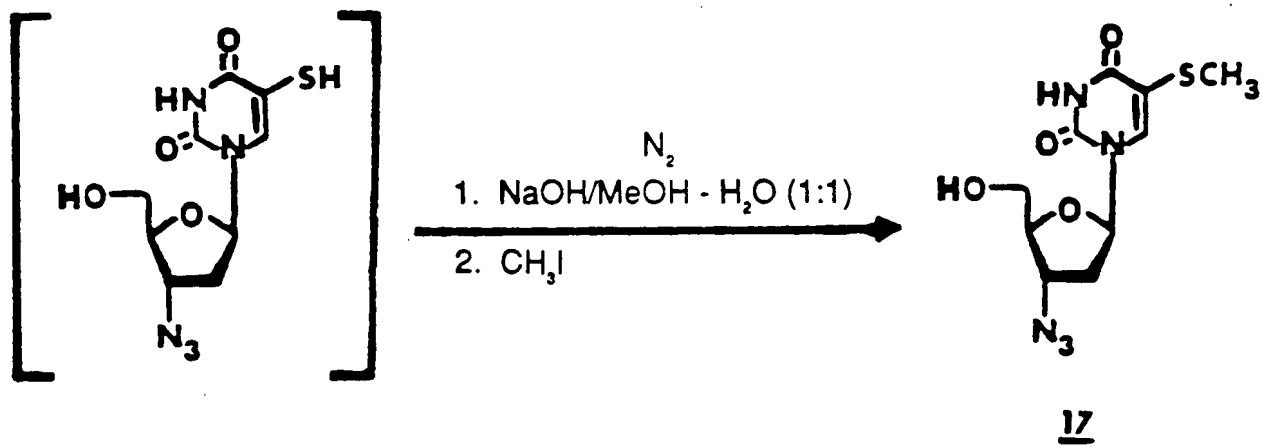
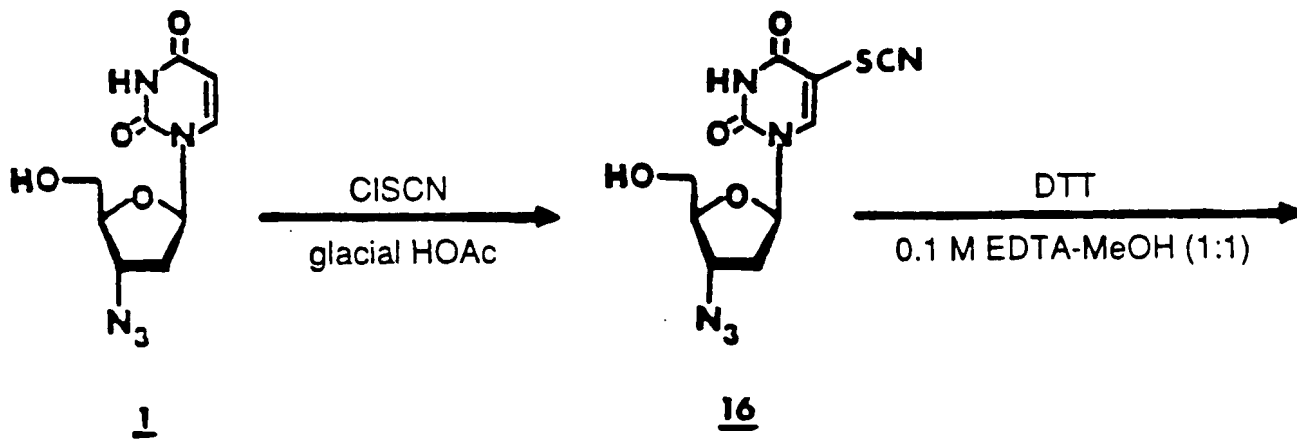
Scheme 2



$\text{R}' = \text{CH}_3, \text{CH}_2\text{CH}_3, \text{CH}_2\text{C}\equiv\text{CH}, \text{CH}_2\text{CH}=\text{CH}_2, \text{CH}_2\text{CN}$

$\chi = \text{OCH}_3, \text{OCH}_2\text{CH}_3, \text{OCH}_2\text{C}\equiv\text{CH}, \text{OCH}_2\text{CH}=\text{CH}_2, \text{OCH}_2\text{CN}$

Scheme 3



Scheme 4

